VENOFER - iron sucrose injection
AMERICAN REGENT, INC.

Rx Only

DESCRIPTION

Venofer® (iron sucrose injection, USP) is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 – 60,000 daltons and a proposed structural formula:

$$[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$$

where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide.

Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer® is available in 5 mL single dose vials (100 mg elemental iron per 5 mL) and 10 mL single dose vials (200 mg elemental iron per 10 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5-11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.
Therapeutic class: Hematinic

CLINICAL PHARMACOLOGY

Pharmacodynamics: Following intravenous administration of Venofer®, iron sucrose is dissociated by the reticuloendothelial system into iron and sucrose. In 22 hemodialysis patients on erythropoietin (recombinant human erythropoietin) therapy treated with iron sucrose containing 100 mg of iron, three times weekly for three weeks, significant increases in serum iron and serum ferritin and significant decreases in total iron binding capacity occurred four weeks from the initiation of iron sucrose treatment.
Pharmacokinetics: In healthy adults treated with intravenous doses of Venofer®, its iron component exhibits first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, non-steady state apparent volume of distribution of 10.0 L and steady state apparent volume of distribution of 7.9 L. Since iron disappearance from serum depends on the need for iron in the iron stores and iron utilizing tissues of the body, serum clearance of iron is expected to be more rapid in iron deficient patients treated with Venofer® as compared to healthy individuals. The effects of age and gender on the pharmacokinetics of Venofer® have not been studied.

Venofer® is not dialyzable through CA210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In *in vitro* studies, the amount of iron sucrose in the dialysate fluid was below the levels of detection of the assay (less than 2 parts per million).
Distribution: In healthy adults receiving intravenous doses of Venofer®, its iron component appears to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating Venofer® containing 100 mg of iron labeled with $^{52}Fe/^{59}Fe$ in patients with iron deficiency shows that a significant amount of the administered iron distributes in the liver, spleen and bone marrow and that the bone marrow is an iron trapping compartment and not a reversible volume of distribution.

Metabolism and Elimination: Following intravenous administration of Venofer®, iron sucrose is dissociated into iron and sucrose by the reticuloendothelial system. The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single intravenous dose of Venofer® containing 1,510 mg of sucrose and 100 mg of iron in 12 healthy adults (9 female, 3 male: age range 32-52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Some iron also is eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration [1]. In this study and another study evaluating a single intravenous dose of iron sucrose containing 500-700 mg of iron in 26 anemic patients on erythropoietin therapy (23 female, 3 male; age range 16-60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level [2].

Drug-drug Interactions: Drug-drug interactions involving Venofer® have not been studied. However, like other parenteral iron preparations, Venofer® may be expected to reduce the absorption of concomitantly administered oral iron preparations.

CLINICAL TRIALS

Venofer® is used to replenish body iron stores in non-dialysis dependent-chronic kidney disease (NDD-CKD) patients receiving erythropoietin and in NDD-CKD patients not receiving erythropoietin, and in hemodialysis dependent-chronic kidney disease (HDD-CKD) and peritoneal dialysis dependent-chronic kidney disease (PDD-CKD) patients receiving erythropoietin. Iron deficiency may be caused by blood loss during dialysis, increased erythropoiesis secondary to erythropoietin use, and insufficient absorption of iron from the gastrointestinal tract. Iron is essential to the synthesis of hemoglobin to maintain oxygen transport and to the function and formation of other physiologically important heme and non-heme compounds. Most dialysis patients require intravenous iron to maintain sufficient iron stores.

Six clinical trials were conducted to assess the safety and efficacy of Venofer®. Five studies were conducted in the United States (516 patients) and one was conducted in South Africa (131 patients).

Study A: Hemodialysis Dependent-Chronic Kidney Disease (HDD–CKD)

Study A was a multicenter, open-label, historically-controlled study in 101 hemodialysis patients (77 patients with Venofer® treatment and 24 in the historical control group) with iron deficiency anemia. Eligibility for Venofer® treatment included patients undergoing chronic hemodialysis three times weekly, receiving erythropoietin, hemoglobin concentration greater than 8.0 and less than 11.0 g/dL for at least two consecutive weeks, transferrin saturation < 20%, and serum ferritin < 300 ng/mL. The mean age of the patients in the treatment group was 65 years with the age range being 31 to 85 years of age. The erythropoietin dose was to be held constant throughout the study. The protocol did not require administration of a test dose; however, some patients received a test dose at the physician's discretion. Exclusion criteria included significant underlying disease, asthma, active inflammatory disease, or serious bacterial or viral infection. Venofer® 5 mL containing 100 mg of elemental iron was administered through the dialysis line at each dialysis session either as slow injection or a saline diluted slow infusion for a total of 10 dialysis sessions with a cumulative dose of 1,000 mg elemental iron. A maximum of 15 mLs (300 mg of elemental iron) of Venofer® was administered per week.
No additional iron preparations were allowed until after the Day 57 evaluation. The mean change in hemoglobin from baseline to Day 24 (end of treatment), Day 36, and Day 57 was assessed. The historical control population consisted of 24 patients with similar ferritin levels as patients treated with Venofer®, who were off intravenous iron for at least 2 weeks and who had received erythropoietin therapy with hematocrit averaging 31-36 for at least two months prior to study entry. The mean age of patients in the historical control group was 56 years, with an age range of 29 to 80 years. Patient age and serum ferritin level were similar between treatment and historical control patients. Of the 77 patients in the treatment group, 44 (57%) were male and 33 (43%) were female. The mean baseline hemoglobin and hematocrit, were higher and erythropoietin dose was lower in the historical control population than the Venofer® treated population.

Patients in the Venofer® treated population showed a statistically significantly greater increase in hemoglobin and hematocrit than did patients in the historical control population. See Table 1.

Table 1. Changes from Baseline in Hemoglobin and Hematocrit

Efficacy parameters	**End of treatment**		**2 week follow-up**		**5 week follow-up**	
	Venofer® (n=69)	**Historical Control (n=18)**	**Venofer® (n=73)**	**Historical Control (n=18)**	**Venofer® (n=71)**	**Historical Control (n=15)**
Hemoglobin (g/dL)	1.0±0.12**	0.0±0.21	1.3±0.14**	-0.6±0.24	1.2±0.17*	-0.1±0.23
Hematocrit (%)	3.1±0.37**	-0.3±0.65	3.6±0.44**	-1.2±0.76	3.3±0.54	0.2±0.86

**p<0.01 and *p<0.05 compared to historical control from ANCOVA analysis with baseline hemoglobin, serum ferritin and erythropoietin dose as covariates.

Serum ferritin increased significantly (p=0.0001) at endpoint of study from baseline in the Venofer®-treated population (165.3±24.2 ng/mL) compared to the historical control population (-27.6±9.5 ng/mL). Transferrin saturation also increased significantly (p=0.0016) at endpoint of study from baseline in the Venofer®-treated population (8.8±1.6%) compared to this historical control population (-5.1±4.3%) [3].

Study B: Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Study B was a multicenter, open label study of Venofer® (iron sucrose injection, USP) in 23 iron deficient hemodialysis patients who had been discontinued from iron dextran due to intolerance. Eligibility criteria and Venofer® administration were otherwise identical to Study A. The mean age of the patients in this study was 53 years, with ages ranging from 21-79 years. Of the 23 patients enrolled in the study, 10 (44%) were male and 13 (56%) were female. The ethnicity breakdown of patients enrolled in this study was as follows: Caucasian (35%); Black (35%); Hispanic (26%); Asian (4%). The mean change from baseline to the end of treatment (Day 24) in hemoglobin, hematocrit, and serum iron parameters was assessed.
All 23 enrolled patients were evaluated for efficacy. Statistically significant increases in mean hemoglobin (1.1±0.2 g/dL), hematocrit (3.6±0.6%), serum ferritin (266.3±30.3 ng/mL) and transferrin saturation (8.7±2.0%) were observed from baseline to end of treatment [4].

Study C: Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Study C was a multicenter, open-label, two period (treatment followed by observation period) study in iron deficient hemodialysis patients. Eligibility for this study included chronic hemodialysis patients with a hemoglobin less than or equal to 10 g/dL, a serum transferrin saturation less than or equal to 20%, and a serum ferritin less than or equal to 200 ng/mL, who were undergoing maintenance hemodialysis 2 to 3 times weekly. The mean age of the patients enrolled in this study was 41 years, with ages ranging from 16-70 years. Of 130 patients evaluated for efficacy in this study, 68 (52%) were male and 62 (48%) were female. The ethnicity breakdown of patients enrolled in this study was as follows: Caucasian (23%); Black (23%); Asian (5%); Other (mixed ethnicity)

(49%). Forty-eight percent of the patients had previously been treated with oral iron. Exclusion criteria were similar to those in studies A and B. Venofer® was administered in doses of 100 mg during sequential dialysis sessions until a pre-determined (calculated) total dose of iron was administered.

Patients received Venofer® at each dialysis session, two to three times weekly. One hour after the start of each session, 5 mL iron sucrose (100 mg iron) in 100 mL 0.9% NaCl was administered into the hemodialysis line. A 50 mg dose (2.5 mL) was given to patients within two weeks of study entry. Patients were treated until they reached an individually calculated total iron dose based on baseline hemoglobin level and body weight. Twenty-seven patients (20%) were receiving erythropoietin treatment at study entry and they continued to receive the same erythropoietin dose for the duration of the study.
Changes from baseline to observation week 2 and observation week 4 (end of study) were analyzed.
The modified intention-to-treat population consisted of 131 patients. Significant ($p<0.0001$) increases from baseline in mean hemoglobin (1.7 g/dL), hematocrit (5%), serum ferritin (434.6 ng/mL), and serum transferrin saturation (14%) were observed at week 2 of the observation period and these values remained significantly increased ($p<0.0001$) at week 4 of the observation period.

Study D: Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD)
Study D was a randomized, open-label, multicenter, active–controlled study of the safety and efficacy of oral iron versus intravenous iron sucrose (Venofer®) in NDD-CKD patients with or without erythropoietin therapy. Erythropoietin therapy was stable for 8 weeks prior to randomization. In the study 188 patients with NDD-CKD, transferrin saturation ≤ 25%, ferritin ≤ 300 ng/mL and an average baseline hemoglobin of ≤ 11.0 g/dL were randomized to receive oral iron (325 mg ferrous sulfate three times daily for 56 days); or Venofer® (either 200 mg over 2-5 minutes 5 times within 14 days or two 500 mg infusions on Day 1 and Day 14, administered over 3.5-4 hours). Of the 188 randomized patients, 182 were treated and followed for up to 56 days. Efficacy assessments were measured on days 14, 28, 42 and 56. The mean age of the 91 treated patients in the Venofer® group was 61.6 years (range 25 to 86 years) and 64 years (range 21 to 86 years) for the 91 patients in the oral iron group. Ethnicity breakdown of the patients in the Venofer® group was as follows: Caucasian (60.4%), Black (34.1%), Hispanic (3.3%), Other (2.2%). Ethnicity breakdown for the oral iron group was: Caucasian (50.5%), Black (44.0%), Hispanic (4.4%), Other (1.1%). Patient demographic characteristics were not significantly different between the groups. A statistically significantly greater proportion of Venofer® subjects (35/79; 44.3%) compared to oral iron subjects (23/82; 28%) had an increase in hemoglobin≥1 g/dL at anytime during the study ($p= 0.03$). In patients ≥ 65 years of age, the proportion of subjects achieving ≥ 1.0 g/dL increase in hemoglobin from baseline was 53% (20/38) in the Venofer® group compared to 23% (10/43) in the oral iron group. In patients <65 years of age, the proportion of subjects achieving ≥ 1.0 g/dL increase in hemoglobin from baseline was 37% (15/41) in the Venofer® group compared to 33% (13/39) in the oral iron group. A statistically significantly greater proportion of Venofer® treated patients (31/79; 39.2%) compared to oral iron treated patients (1/82; 1.2%) had an increase in hemoglobin ≥1 g/dL and ferritin ≥160 ng/mL at anytime during the study ($p<0.0001$).

Study E: Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD)
Study E was a randomized [2:1 treatment: control], open-label, multicenter study comparing PDD-CKD patients receiving an erythropoietin and IV iron to PDD-CKD patients receiving an erythropoietin alone without iron supplementation. 126 patients with PDD-CKD, stable erythropoietin for 8 weeks, TSAT≤25%, Ferritin ≤500 ng/mL and an average baseline hemoglobin of ≤11.5 g/dL were randomized to receive either no iron or Venofer® (iron sucrose injection, USP) (300 mg in 250 mL 0.9% NaCl over 1.5 hours on Day 1 and 15 and 400 mg in 250 mL 0.9% NaCl over 2.5 hours on Day 29). 121 of the 126 randomized patients were treated and followed for up to 71 days with a total of 88 patients who completed the study. Efficacy assessments were measured on days 15, 29, 43, 57 and 71. Patient demographic characteristics were not significantly different between the groups. The mean age of the 75 treated patients in the Venofer® / erythropoietin group was 51.9 years (range 21 to 81 years) vs. 52.8 years (range 23 to 77 years) for 46 patients in the erythropoietin alone group. Ethnicity breakdown of the patients in the Venofer® / erythropoietin group was as follows: Caucasian (36%); Hispanic (32 %); Black (21.3%); Other (10.7%). Ethnicity breakdown for the erythropoietin alone group was: Hispanic (43.5%); Caucasian (30.4%); Black (15.2%); Other (10.9%). Patients in the Venofer® / erythropoietin group had statistically significantly greater mean change from baseline to the highest hemoglobin value (1.3 g/dL), compared to subjects who received erythropoietin alone (0.6 g/dL) ($p<0.01$). A statistically significantly greater proportion of subjects treated with Venofer® / erythropoietin (59.1 %) had an increase in hemoglobin of ≥1 g/dL at any time during the study compared to the subjects who received erythropoietin only (33.3%) ($p < 0.05$).

CLINICAL INDICATIONS AND USAGE

Venofer® is indicated in the treatment of iron deficiency anemia in the following patients:
- non-dialysis dependent-chronic kidney disease (NDD-CKD) patients receiving an erythropoietin

- non-dialysis dependent-chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin

- hemodialysis dependent-chronic kidney disease (HDD-CKD) patients receiving an erythropoietin
- peritoneal dialysis dependent-chronic kidney disease (PDD-CKD) patients receiving an erythropoietin.

CONTRAINDICATIONS

The use of Venofer® is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to Venofer® or any of its inactive components, and in patients with anemia not caused by iron deficiency.

WARNINGS

Hypersensitivity reactions have been reported with injectable iron products. See **PRECAUTIONS** and **ADVERSE REACTIONS.**

PRECAUTIONS

General:

Because body iron excretion is limited and excess tissue iron can be hazardous, caution should be exercised to withhold iron administration in the presence of evidence of tissue iron overload. Patients receiving Venofer® require periodic monitoring of hematologic and hematinic parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Iron therapy should be withheld in patients with evidence of iron overload. Transferrin saturation values increase rapidly after IV administration of iron sucrose; thus, serum iron values may be reliably obtained 48 hours after IV dosing. (See **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**).

Hypersensitivity Reactions:

Serious hypersensitivity reactions have been reported in patients receiving Venofer®. No life-threatening hypersensitivity reactions were observed in the clinical studies. Several cases of mild or moderate hypersensitivity reactions were observed in these studies. There are post-marketing spontaneous reports of life-threatening hypersensitivity reactions in patients receiving Venofer. See **ADVERSE REACTIONS.**

Hypotension:

Hypotension has been reported frequently in hemodialysis dependent chronic kidney disease patients receiving intravenous iron. Hypotension also has been reported in non-dialysis dependent and peritoneal dialysis dependent-chronic kidney disease patients receiving intravenous iron. Hypotension following administration of Venofer® may be related to rate of administration and total dose administered. Caution should be taken to administer Venofer® according to recommended guidelines. See **DOSAGE AND ADMINISTRATION**

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of Venofer®.

Venofer® was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test.

Venofer® at IV doses up to 15 mg iron/kg/day (about 1.2 times the recommended maximum human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy Category B:

Teratology studies have been performed in rats at IV doses up to 13 mg iron/kg/day (about 0.5 times the recommended maximum human dose on a body surface area basis) and rabbits at IV doses up to 13 mg iron/kg/day (about 1 times the recommended maximum human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Venofer®. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

Venofer® is excreted in milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Venofer® is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness of Venofer® in pediatric patients have not been established. In a country where Venofer® is available for use in children, at a single site, five premature infants (weight less than 1,250 g) developed necrotizing enterocolitis and two of the five expired during or following a period when they received Venofer®, several other medications and erythropoietin. Necrotizing

enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to Venofer® or any other drugs could be established.

Geriatric Use:
Studies A through E did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the 1,051 patients in two post-marketing safety studies of Venofer®, 40% were 65 years and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Events observed in all treated populations

The frequency of adverse events associated with the use of Venofer® has been documented in six randomized clinical trials involving 231 hemodialysis dependent, 139 non-dialysis dependent and 75 peritoneal dialysis dependent-CKD patients; and in two post-marketing safety studies involving 1,051 hemodialysis dependent-CKD patients for a total of 1,496 patients. In addition, over 2,000 patients treated with Venofer® have been reported in the medical literature.
Treatment-emergent adverse events reported by ≥ 2% of treated patients in the randomized clinical trials, whether or not related to Venofer® administration, are listed by indication in Table 2.
Table 2. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients By Clinical Indication (Multidose Safety Population)

Adverse Events (Preferred Term)	HDD-CKD	NDD-CKD		PDD-CKD	
	Venofer® (N=231) %	Venofer® (N=139) %	Oral Iron (N=139) %	Venofer® (N=75) %	EPO Only (N=46) %
Subjects with any adverse event	78.8	76.3	73.4	72.0	65.2
Ear and Labyrinth Disorders	0	2.2	0.7	0	0
Ear Pain					
Eye Disorders	0.4	0	0	2.7	0
Conjunctivitis					
Gastrointestinal Disorders	3.5	1.4	2.9	4.0	6.5
Abdominal pain NOS*	1.3	4.3	12.9	4.0	6.5
Constipation	5.2	7.2	10.1	8.0	4.3
Diarrhea NOS	0.9	7.9	0	0	0
Dysgeusia	14.7	8.6	12.2	5.3	4.3
Nausea	9.1	5.0	8.6	8.0	2.2
Vomiting NOS					
General Disorders and	2.2	0.7	2.2	2.7	0
Administration Site Conditions	6.1	1.4	0	2.7	0
Asthenia	0.4	6.5	6.5	0	2.2
Chest pain	1.7	3.6	5.8	0	4.3
Edema NOS	3.0	0	0	0	0
Fatigue	0	3.6	0	0	0
Feeling abnormal	0	2.2	0	0	0
Infusion site burning	0	2.2	0	0	0
Injection site extravasation	2.6	7.2	5.0	5.3	10.9
Injection site pain	3.0	0.7	0.7	1.3	0
Peripheral edema					
Pyrexia					
Infections and Infestations	0	0	0	4.0	8.7
Catheter site infection	0.9	0.7	2.2	2.7	2.2
Nasopharyngitis	0	0	0	8.0	10.9
Peritoneal infection	0	0.7	0.7	4.0	0
Sinusitis NOS	1.3	0.7	1.4	2.7	2.2
Upper respiratory tract infection NOS	0.4	0.7	5.0	1.3	2.2
Urinary tract infection NOS					

Injury, Poisoning and Procedural Complications	9.5	1.4	0	0	0
Graft complication					
Investigations	0.4	2.2	2.2	0	0
Cardiac murmur NOS	0	1.4	3.6	2.7	4.3
Fecal occult blood positive					
Metabolism and Nutrition Disorders	3.0	1.4	0.7	1.3	0
Fluid overload	0	2.9	1.4	0	0
Gout	0	2.9	0	0	2.2
Hyperglycemia NOS	0.4	0.7	0.7	4.0	0
Hypoglycemia NOS					
Musculoskeletal and Connective	3.5	1.4	2.2	4.0	4.3
Tissue Disorders	0	0	0	0	4.3
Arthralgia	2.2	2.2	3.6	1.3	4.3
Arthritis NOS	29.4	0.7	0.7	2.7	0
Back pain	0	3.6	0	1.3	0
Muscle cramp	5.6	4.3	0	2.7	6.5
Myalgia					
Pain in extremity					
Nervous System Disorders	6.5	6.5	1.4	1.3	4.3
Dizziness	12.6	2.9	0.7	4.0	0
Headache	0	0.7	0.7	0	4.3
Hypoesthesia					
Respiratory, Thoracic and	3.0	2.2	0.7	1.3	0
Mediastinal Disorders	3.5	3.6	0.7	1.3	2.2
Cough	0	2.2	0.7	0	0
Dyspnea	0	1.4	2.2	1.3	0
Dyspnea exacerbated	0.4	0	0	6.7	0
Nasal congestion	0	0.7	2.2	0	0
Pharyngitis					
Rhinitis allergic NOS					
Skin and Subcutaneous	3.9	2.2	4.3	2.7	0
Tissue Disorders	0.4	1.4	2.2	0	2.2
Pruritus					
Rash NOS					
Vascular Disorders	6.5	6.5	4.3	8.0	6.5
Hypertension NOS	39.4	2.2	0.7	2.7	2.2
Hypotension NOS					

*NOS=Not otherwise specified

Treatment-emergent adverse events reported in ≥ 2% of patients by dose group are shown in Table 3.

Table 3. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients by Dose Group (Multidose Safety Population)

Adverse Events (Preferred Term)	**HDD-CKD**	**NDD-CKD**		**PDD-CKD**
	100 mg (N=231) %	**200 mg (N=109) %**	**500 mg (N=30) %**	**300 mg for 2 doses followed by 400 mg for 1 dose (N=75) %**
Subjects with any adverse event	78.8	75.2	80.0	72.0
Ear and Labyrinth Disorders				
Ear pain	0	0.9	6.7	0
Eye Disorders	0.4	0	0	2.7
Conjunctivitis				
Gastrointestinal Disorders				

Abdominal pain NOS*	3.5	1.8	0	4.0
Constipation	1.3	3.7	6.7	4.0
Diarrhea NOS	5.2	6.4	10.0	8.0
Dysgeusia	0.9	9.2	3.3	0
Nausea	14.7	9.2	6.7	5.3
Vomiting NOS	9.1	5.5	3.3	8.0
General Disorders and Administration Site Conditions				
Asthenia	2.2	0.9	0	2.7
Chest pain	6.1	0.9	3.3	2.7
Edema NOS	0.4	7.3	3.3	0
Fatigue	1.7	4.6	0	0
Feeling abnormal	3.0	0	0	0
Infusion site burning	0	3.7	3.3	0
Injection site pain	0	2.8	0	0
Peripheral edema	2.6	5.5	13.3	5.3
Pyrexia	3.0	0.9	0	1.3
Infections and Infestations				
Catheter site infection	0	0	0	4.0
Nasopharyngitis	0.9	0.9	0	2.7
Peritoneal infection	0	0	0	8.0
Sinusitis NOS	0	0	3.3	4
Upper respiratory tract infection	1.3	0.9	0	2.7
Injury, Poisoning and Procedural Complications				
Graft complication	9.5	1.8	0	0
Investigations				
Cardiac murmur NOS	0.4	2.8	0	0
Fecal occult blood positive	0	1.8	0	2.7
Metabolism and Nutrition Disorders				
Fluid overload	3.0	1.8	0	1.3
Gout	0	1.8	6.7	0
Hyperglycemia NOS	0	3.7	0	0
Hypoglycemia NOS	0.4	0.9	0	4.0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	3.5	0.9	3.3	4.0
Back pain	2.2	1.8	3.3	1.3
Muscle cramp	29.4	0	3.3	2.7
Myalgia	0	2.8	6.7	1.3
Pain in extremity	5.6	4.6	3.3	2.7
Nervous System Disorders				
Dizziness	6.5	5.5	10.0	1.3
Headache	12.6	3.7	0	4.0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3.0	0.9	6.7	1.3
Dyspnea	3.5	1.8	10.0	1.3
Pharyngitis	0.4	0	0	6.7
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.9	0.9	6.7	2.7
Vascular Disorders				
Hypertension NOS	6.5	6.4	6.7	8.0
Hypotension NOS	39.4	0.9	6.7	2.7

*NOS=Not otherwise specified

Drug related adverse events reported by ≥ 2% of Venofer® treated patients are shown by dose group in Table 4.

Table 4. Most Common Adverse Events Related to Study Drug Reported in ≥ 2% of Patients by Dose Group (Multidose Safety Population)

Adverse Events (Preferred Term)	HDD-CKD	NDD-CKD		PDD-CKD
	100 mg (N=231) %	200 mg (N=109) %	500 mg (N=30) %	300 mg for 2 doses followed by 400 mg for 1 dose (N= 75) %
Subjects with any adverse event	14.7	23.9	20.0	10.7
Gastrointestinal Disorders				
Diarrhea NOS*	0.9	0	0	2.7
Dysgeusia	0.9	7.3	3.3	0
Nausea	1.7	2.8	0	1.3
General Disorders and Administration Site Conditions				
Infusion site burning	0	3.7	0	0
Injection site pain	0	2.8	0	0
Peripheral edema	0	1.8	6.7	0
Nervous Systems Disorders				
Dizziness	0	2.8	6.7	0
Headache	0	2.8	0	0
Vascular Disorders				
Hypotension NOS	5.2	0	6.7	0

*NOS=Not otherwise specified

Adverse Events Observed in Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD) Patients

Adverse reactions, whether or not related to Venofer® (iron sucrose injection, USP) administration, reported by >5% of treated patients from a total of 231 patients in HDD-CKD Studies A, B, and C were as follows: hypotension (39.4%), muscle cramps (29.4%), nausea (14.7%), headache (12.6%), graft complications (9.5%), vomiting (9.1%), dizziness (6.5%), hypertension (6.5%), chest pain (6.1%), and diarrhea (5.2%).

In the first post-marketing safety study, 665 chronic hemodialysis patients were treated with Venofer® doses of 100 mg at each dialysis session for up to 10 consecutive dialysis sessions for their iron deficiency or on a weekly basis for 10 weeks for maintenance of iron stores. In this study, 72% of the patients received up to 10 doses, 27% received between 11-30 doses, and 1% received 40 to 50 doses of Venofer®. Serious adverse events and drug-related non-serious adverse events were collected. In the second post-marketing safety study, 386 hemodialysis patients were exposed to a single dose of Venofer® (100 mg IV by slow injection over 2 minutes or 200 mg IV by slow injection over 5 minutes). The mean age of patients enrolled into the two post-marketing safety studies was 59 years, with a range of 20-93 years. Males made up 60% of the population. The ethnicity of the patients enrolled in the two studies included Blacks (44%), Caucasians (41%), Hispanics (11%), Asians (3%), and others (1%). Adverse events reported by > 1% of 1,051 treated patients were: cardiac failure congestive, sepsis NOS and dysgeusia.

Adverse Events Observed in Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD) Patients

In Study D of 182 treated NDD-CKD patients, 91 were exposed to Venofer®. Adverse events, whether or not related to Venofer® , reported by ≥5% of the Venofer® exposed patients were as follows: dysgeusia (7.7%), peripheral edema (7.7%), diarrhea (5.5%), constipation (5.5%), nausea (5.5%), dizziness (5.5%), and hypertension (5.5%). One serious related adverse reaction was reported (hypotension and shortness of breath not requiring hospitalization in a Venofer® patient). Two patients experienced possible hypersensitivity/allergic reactions (local edema/hypotension) during the study. Of the 5 patients who prematurely discontinued the

treatment phase of the study due to adverse events (2 oral iron group and 3 Venofer® group), three Venofer® patients had events that were considered drug-related (hypotension, dyspnea and nausea).

In an additional study of Venofer® with varying erythropoietin doses in 96 treated NDD-CKD patients, adverse events, whether or not related to Venofer® reported by ≥5% of Venofer® exposed patients are as follows: diarrhea (16.5%), edema (16.5%), nausea (13.2%), vomiting (12.1%), arthralgia (7.7%), back pain (7.7%), headache (7.7%), hypertension (7.7%), dysgeusia (7.7%), dizziness (6.6%), extremity pain (5.5%), and injection site burning (5.5%). No patient experienced a hypersensitivity/allergic reaction during the study. Of the patients who prematurely discontinued the treatment phase of the study due to adverse events (2.1% oral iron group and 12.5% Venofer® group), only one patient (Venofer® group) had events that were considered drug-related (anxiety, headache, and nausea).

Ninety-one (91) patients in this study were exposed to Venofer® either during the treatment or extended follow-up phase.

Adverse Events Observed in Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD) Patients

In Study E of 121 treated PDD-CKD patients, 75 patients were exposed to Venofer®. Adverse events, whether or not related to Venofer® reported by ≥5% of these patients are as follows: diarrhea, peritoneal infection, vomiting, hypertension, pharyngitis, peripheral edema and nausea.

In these 75 patients exposed to Venofer®, 9 patients experienced serious adverse events as follows: peritoneal infection (2 patients) and 1 patient each with cardiopulmonary arrest, myocardial infarction, upper respiratory infection NOS, anemia, gangrene, hypovolemia and tuberculosis. None of these events were considered drug-related. Two Venofer® patients experienced a moderate hypersensitivity/allergic reaction (rash or swelling/itching) during the study.

The only drug related adverse reaction to Venofer® administration reported by ≥2% of patients was diarrhea.

Three patients in the Venofer® study group discontinued study treatment due to adverse events (cardiopulmonary arrest, peritonitis and myocardial infarction, hypertension) which were considered to be not drug-related.

Hypersensitivity Reactions:

See **WARNINGS** and **PRECAUTIONS.**

In clinical studies, several patients experienced hypersensitivity reactions presenting with wheezing, dyspnea, hypotension, rashes, or pruritus. Serious episodes of hypotension occurred in 2 patients treated with Venofer® at a dose of 500 mg.

The post-marketing spontaneous reporting system includes reports of patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion) associated with Venofer® administration.

One hundred thirty (11%) of the 1,151 patients evaluated in the 4 U.S. trials in HDD-CKD patients (studies A, B and the two post marketing studies) had prior other intravenous iron therapy and were reported to be intolerant (defined as precluding further use of that iron product). When these patients were treated with Venofer® there were no occurrences of adverse events that precluded further use of Venofer®.

OVERDOSAGE

Dosages of Venofer® (iron sucrose injection, USP) in excess of iron needs may lead to accumulation of iron in storage sites leading to hemosiderosis. Periodic monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognizing iron accumulation. Venofer® should not be administered to patients with iron overload and should be discontinued when serum ferritin levels equal or exceed established guidelines [5]. Particular caution should be exercised to avoid iron overload where anemia unresponsive to treatment has been incorrectly diagnosed as iron deficiency anemia.

Symptoms associated with overdosage or infusing Venofer® too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. Most symptoms have been successfully treated with IV fluids, hydrocortisone, and/or antihistamines. Infusing the solution as recommended or at a slower rate may also alleviate symptoms.

Preclinical Data:

Single IV doses of Venofer® at 150 mg iron/kg in mice (about 3 times the recommended maximum human dose on a body surface area basis) and 100 mg iron/kg in rats (about 8 times the recommended maximum human dose on a body surface area basis) were lethal.

The symptoms of acute toxicity were sedation, hypoactivity, pale eyes, and bleeding in the gastrointestinal tract and lungs.

DOSAGE AND ADMINISTRATION

The dosage of Venofer® is expressed in terms of mg of elemental iron. Each mL contains 20 mg of elemental iron.

Most CKD patients will require a minimum cumulative repletion dose of 1,000 mg of elemental iron, administered over sequential sessions, to achieve a favorable hemoglobin response and to replenish iron stores (ferritin, TSAT). Hemodialysis patients may

continue to require therapy with Venofer® or other intravenous iron preparations at the lowest dose necessary to maintain target levels of hemoglobin, and laboratory parameters of iron storage within acceptable limits.

Administration: Venofer® must only be administered intravenously either by slow injection or by infusion.

Recommended Adult Dosage:

Hemodialysis Dependent-Chronic Kidney Disease Patients (HDD-CKD): Venofer® may be administered undiluted as a 100 mg slow intravenous injection over 2 to 5 minutes or as an infusion of 100 mg, diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes per consecutive hemodialysis session for a total cumulative dose of 1,000 mg.

Non-Dialysis Dependent-Chronic Kidney Disease Patients (NDD-CKD): Venofer® is administered as a total cumulative dose of 1,000 mg over a 14 day period as a 200 mg slow IV injection undiluted over 2 to 5 minutes on 5 different occasions within the 14 day period. There is limited experience with administration of an infusion of 500 mg of Venofer®, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5-4 hours on day 1 and day 14; hypotension occurred in 2 of 30 patients treated. (See **CLINICAL TRIALS, Study D: Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD) Patients** and **ADVERSE REACTIONS, Adverse Events Observed in Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Patients sections**.)

Peritoneal Dialysis Dependent-Chronic Kidney Disease Patients (PDD-CKD): Venofer® is administered as a total cumulative dose of 1,000 mg in 3 divided doses, given by slow intravenous infusion, within a 28 day period: 2 infusions of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. The Venofer® dose should be diluted in a maximum of 250 mL of 0.9% NaCl.

HOW SUPPLIED

Venofer® is supplied in 5 mL and 10 mL single dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL) and each 10 mL vial contains 200 mg elemental iron (20 mg/mL). Contains no preservatives. Store in original carton at 25°C (77°F). Excursions permitted to 15°-30°C (59°-86°F). [See the USP controlled room temperature]. Do not freeze.
Sterile

NDC-0517-2340-01	100 mg/5 mL Single Dose Vial	Individually Boxed
NDC-0517-2340-10	100 mg/5 mL Single Dose Vial	Packages of 10
NDC-0517-2340-25	100 mg/5 mL Single Dose Vial	Packages of 25
NDC-0517-2310-01	200 mg/10 mL Single Dose Vial	Individually Boxed
NDC-0517-2310-05	200 mg/10 mL Single Dose Vial	Packages of 5
NDC-0517-2310-10	200 mg/10 mL Single Dose Vial	Packages of 10

Rx Only

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SHIRLEY, NY 11967
IN2340
Rev. 11/07
MG #15727

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